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     FILE 'REGISTRY' ENTERED AT 15:31:30 ON 08 MAY 2000
                E "D-LYSINE"/CN 5
L1              1 S E3
                E "POLY-D-LYSINE"/CN 5
                E "POLY-L-LYSINE"/CN 5
L2              2 S E3
L3              3 S L1 OR L2

     FILE 'CAPLUS' ENTERED AT 15:32:06 ON 08 MAY 2000
L1              1 SEA FILE=REGISTRY ABB=ON  PLU=ON  D-LYSINE/CN
L2              2 SEA FILE=REGISTRY ABB=ON  PLU=ON  POLY-L-LYSINE/CN
L3              3 SEA FILE=REGISTRY ABB=ON  PLU=ON  L1 OR L2
L4          20986 SEA FILE=CAPLUS ABB=ON  PLU=ON  L3 OR (L OR D)(W)(LYSINE
                  OR LYS)
L5             51 SEA FILE=CAPLUS ABB=ON  PLU=ON  L4 AND (KIDNEY OR
                  RENAL?)(5A)(UPTAK? OR RETEN?)
L6             17 SEA FILE=CAPLUS ABB=ON  PLU=ON  L5 AND ADMIN?

=> d 1-17 .bevstr

L6   ANSWER 1 OF 17  CAPLUS  COPYRIGHT 2000 ACS
ACCESSION NUMBER:         1999:196777  CAPLUS
DOCUMENT NUMBER:          131:113202
TITLE:                    Uptake kinetics of the somatostatin receptor
                          ligand [86Y]DOTA-dPhe1-Tyr3-octreotide
                          ([86Y]SMT487) using positron emission tomography
                          in non-human primates and calculation of
                          radiation doses of the 90Y-labeled analog
AUTHOR(S):                Rosch, Frank; Herzog, Hans; Stolz, Barbara;
                          Brockmann, Jorg; Kohle, Martin; Muhlensiepen,
                          Heinz; Marbach, Peter; Muller-Gartner,
                          Hans-Wilhelm
CORPORATE SOURCE:         Institut fur Nuklearchemie, Forschungszentrum
                          Julich, Germany
SOURCE:                   Eur. J. Nucl. Med. (1999), 26(4), 358-366
                          CODEN: EJNMD9; ISSN: 0340-6997
PUBLISHER:                Springer-Verlag
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   [90Y]DOTA-dPhe1-Tyr3-octreotide ([90Y]-SMT487) has been suggested as
     a promising radiotherapeutic agent for somatostatin
     receptor-expressing tumors.  In order to quantify the in vivo
     parameters of this compd. and the radiation doses delivered to
     healthy organs, the analog [86Y]DOTA-dPhe1-Tyr3-octreotide was
     synthesized and its uptake measured in baboons using positron
     emission tomog. (PET). [86Y]DOTA-dPhe1-Tyr3-octreotide was
     administered at two different peptide concns., namely 2 and
     100 mg peptide per m2 body surface.  The latter concn. corresponded
     to a radiotherapeutic dose.  In a third protocol
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[86Y]DOTA-dPhe1-Tyr3-octreotide was injected in conjunction with a simultaneous infusion of an amino acid soln. that was high in **l-lysine** in order to lower the **renal uptake** of radioyttrium. Quant. whole-body PET scans were recorded to measure the **uptake** kinetics for **kidneys**, liver, lung and bone. The individual abs. uptake kinetics were used to calc. the radiation doses for [90Y]DOTA-dPhe1-Tyr3-octreotide according to the MIRD recommendations extrapolated to a 70-kg human. The highest radiation dose was received by the kidneys, with 2.1-3.3 mGy per MBq [90Y]DOTA-dPhe1-Tyr3-octreotide injected. For the 100 mg/m2 SMT487 protocol with amino acid co-infusion this dose was about 20%-40% lower than for the other two treatment protocols. The liver and the red bone marrow received doses ranging from 0.32 to 0.53 mGy and 0.03 to 0.07 mGy per MBq [90Y]DOTA-dPhe1-Tyr3-octreotide, resp. The av. ED equiv. amounted to 0.23-0.32 mSv/MBq. The comparatively low estd. radiation doses to normal organs support the initiation of clin. phase I trials with [90Y]DOTA-dPhe1-Tyr3-octreotide in patients with somatostatin receptor-expressing tumors.

L6 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1999:65755 CAPLUS
DOCUMENT NUMBER: 130:234053
TITLE: Chemical design of radiolabeled antibody fragments for low renal radioactivity levels
AUTHOR(S): Arano, Yasushi; Fujioka, Yasushi; Akizawa, Hiromichi; Ono, Masahiro; Uehara, Tomoya; Wakisaka, Kouji; Nakayama, Morio; Sakahara, Harumi; Konishi, Junji; Saji, Hideo
CORPORATE SOURCE: Department of Patho-Functional Bioanalysis, Graduate School of Pharmaceutical Sciences, and Department of Nuclear Medicine and Diagnostic Imaging, Graduate School of Medicine, Kyoto University, Kyoto, 606-8501, Japan
SOURCE: Cancer Res. (1999), 59(1), 128-134
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: AACR Subscription Office
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **renal uptake** of radiolabeled antibody fragments presents a problem in targeted imaging and therapy. We hypothesized that the renal radioactivity levels of radiolabeled antibody fragments could be reduced if radiolabeled compds. of urinary excretion were released from glomerularly filtered antibody fragments before they were incorporated into renal cells by the action of brush border enzymes, present on the lumen of renal tubules. 3'-[131I]Iodohippuryl N'-maleoyl-**L-lysine** ([131I]HML) was conjugated with a thiolated Fab fragment because the glycyl-lysine sequence in HML is a substrate

for a brush border enzyme and metaiodohippuric acid is released by cleavage of the linkage. Fab fragments were also radiolabeled by direct radioiodination (125I-Fab) or by conjugation with meta-[125I]-iodohippuric acid via an amide bond [N-(5-maleimidopentyl) 3'-iodohippuric acid amide ([125I]MPH-Fab) or an ester bond [maleimidoethyl 3'-iodohippurate ([125I]MIH-Fab)] by procedures similar to those used for [131I]IML-Fab. [125I]MIH-Fab and 125I-Fab reached their peak ratios of 3.8 and 7.3 at 1 h, resp., and [125I]MPH-Fab showed the max. ratio of 16.8 at 6 h. In subcellular distribution studies, both [125I]MIH-Fab and 125I-Fab showed migration of radioactivity from the membrane to the lysosomal fraction of the renal cells from 10 to 30 min postinjection, whereas the majority of the radioactivity was detected only in the membrane fraction after **administration** of [131I]HML-Fab at both time points. In nude mice, [131I]HML-Fab showed one-quarter of the renal radioactivity of simultaneously **administered** 125I-Fab without impairing the target radioactivity levels 3 h after injection. These findings indicated that HML is a useful reagent for targeted imaging and therapy using antibody fragments as vehicles. These findings also suggested that the radiochem. design of radiolabeled antibody fragments that liberate radiometabolites of urinary excretion from antibody fragments by the action of brush border enzymes may constitute a new strategy for reducing the renal radioactivity levels of antibody fragments.

L6 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:678097 CAPLUS
DOCUMENT NUMBER: 130:49277
TITLE: 90Yttrium-Labeled Complementarity-Determining-Region-Grafted Monoclonal Antibodies for Radioimmunotherapy: Radiolabeling and Animal Biodistribution Studies
AUTHOR(S): Govindan, Serengulam V.; Shih, Lisa B.; Goldenberg, David M.; Sharkey, Robert M.; Karacay, Habibe; Donnelly, Joseph E.; Losman, Michele J.; Hansen, Hans J.; Griffiths, Gary L.
CORPORATE SOURCE: Immunomedics Inc., Morris Plains, NJ, 07950, USA
SOURCE: Bioconjugate Chem. (1998), 9(6), 773-782
CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 90Yttrium-labeled monoclonal antibodies (mAbs) are likely to be important to radioimmunotherapy (RAIT) of a variety of cancers. The goal of this study was to select and evaluate a form of [90Y]mAb suitable for RAIT and det. conditions for high-yield, reproducible radiolabelings. 90Y-Labelings, at 2-40 mCi levels, of cdr-grafted versions of anti-B-cell lymphoma (hLL2) and anti-CEA (hIMMU-14) mAbs were optimized to >90% incorporations using the macrocyclic chelator

DOTA as the metal carrier. In in vitro challenge assays, the stability of mAbs labeled with [90Y]DOTA was better than that of the corresponding [90Y]benzyl-DTPA conjugates. The retention of [90Y]DOTA-hLL2 on Raji tumor cells in vitro was similar to that of the same mAb labeled with [90Y]benzyl-DTPA and was about twice as much as with [125I]hLL2, indicating residualization of metalated mAb. Both [90Y]hLL2 conjugates, prepd. using DOTA and Bz-DTPA, had similar max. tolerated doses of 125 .mu.Ci in BALB/c mice and showed no discernible chelator-induced immune responses. Animal biodistribution studies in nude mice bearing Ramos human B-cell lymphoma xenografts revealed similar tumor and tissue uptake over a 10 day period, with the exception of bone uptake which was up to 50% lower for [88Y]DOTA-hLL2 compared to [88Y]Bz-DTPA-hLL2 at time points beyond 24 h. With [90Y]DOTA-hLL2 fragments, in vivo animal tumor dosimetries were inferior to those for the IgG, and **kidney uptake** was relatively high even with **D-lysine administration**. The ability of [111In]DOTA-hLL2 to accurately predict [90Y]DOTA-hLL2 biodistribution was established. These preclin. findings demonstrate that [90Y]DOTA-(CDR-grafted) mAbs are suitable for examn. in clin. RAIT.

L6 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:253214 CAPLUS
DOCUMENT NUMBER: 128:235080
TITLE: Streptavidin in antibody pretargeting. 2. Evaluation of methods for decreasing localization of streptavidin to kidney while retaining its tumor binding capacity
AUTHOR(S): Wilbur, D. Scott; Hamlin, Donald K.; Buhler, Kent R.; Pathare, Pradip M.; Vessella, Robert L.; Stayton, Patrick S.; To, Richard
CORPORATE SOURCE: Departments of Radiation Oncology Urology and Bioengineering, University of Washington, Seattle, WA, 98195, USA
SOURCE: Bioconjugate Chem. (1998), 9(3), 322-330
CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An investigation was conducted to det. if the kidney localization of recombinant streptavidin can be decreased to improve its characteristics in pretargeting protocols. Three different methods of accomplishing this were evaluated. The 1st method, blocking **kidney uptake** with a preadministration of recombinant streptavidin in which biotin occupied all of the binding sites, was unsuccessful. In a 2nd method, **L-lysine administration** was used to block kidney localization. This method worked well, decreasing the concn. to 29%

of the unmodified amt. at 8 h postinjection. However, this method suffered from a requirement for const. infusion of lysine during the period of observation. A 3rd method, use of succinylated recombinant streptavidin, was the best approach. Succinylation of streptavidin was readily accomplished with very good protein recovery. With the succinylated streptavidin, the kidney concn. was only 14% of that of nonmodified streptavidin at 4 h postinjection. Succinylation of streptavidin improved its distribution characteristics for pretargeting applications. A new water-solubilized biotinidase-stabilized biotinylation reagent was prepd. Using that reagent in a pretargeting expt., an equiv. quantity of succinylated recombinant streptavidin as biotinylated antibody Fab' was localized in a tumor xenograft model. In that expt., the kidney concn. was decreased to <10% of that obtained with unmodified recombinant streptavidin at 24 h postinjection. The fact that succinylated streptavidin has no specific tissue localization should allow its use as a carrier of radioactivity in 2-step pretargeting protocols.

L6 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:41222 CAPLUS
DOCUMENT NUMBER: 128:164448
TITLE: **D-Lysine** reduction of indium-111 octreotide and yttrium-90 octreotide **renal uptake**
AUTHOR(S): Bernard, Bert F.; Krenning, Eric P.; Breeman, Wout A. P.; Rolleman, Edgar J.; Bakker, Willem H.; Visser, Theo J.; Macke, Helmut; De Jong, Marion
CORPORATE SOURCE: Departments of Nuclear Medicine and Internal Medicine III, Erasmus Medical University and Academic Hospital Dijkzigt, Rotterdam, 3015 GD, Neth.
SOURCE: J. Nucl. Med. (1997), 38(12), 1929-1933
CODEN: JNMEAQ; ISSN: 0161-5505
PUBLISHER: Society of Nuclear Medicine
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Indium-111-DTPA-octreotide (111In-DTPAOC) is used successfully for imaging somatostatin receptor-pos. lesions. A new and promising application is its use in peptide-receptor radionuclide therapy (PRRT). For the latter purpose, [DOTA0,D-Phe1,Tyr3]octreotide (DOTATOC), which is suitable for stable radiolabeling with 90Y, is probably even more promising. Significant **renal uptake** of these octreotide analogs exists, however, reducing the scintigraphic sensitivity for detection of small tumors in the perirenal region and limiting the possibilities for PRRT. We showed that the **renal uptake** of 111In-DTPAOC could be reduced to about 50% of control by **L-lysine**

administrati n in vivo in rats. This study compares the effects of several doses and different methods of **administration** of D- and **L-lysine**, in addn. to time-related effects of **D-lysine**, on **kidney uptake** of 111In-DTPAOC and 90Y-DOTATOC. Male Wistar rats (200-250 g) were given 111In-DTPAOC (0.2 MBq, 0.5 .mu.g-0.5 mg i.v., i.p. or orally) in the presence or absence of D- or **L-lysine**. At 1, 4 or 24 h, the rats were killed, and the organs were isolated and counted for radioactivity. In different expts., male Wistar rats (200-250 g) were given 90Y-DOTATOC (1 MBq, 0.5 .mu.g i.v.) in the presence or absence of **D-lysine**. At 24 h, the rats were killed, and the organs were isolated and counted for radioactivity. **Administration** of D- or **L-lysine** in a single i.v. dose of 400 mg/kg, resulted in more than 50% inhibition of **kidney uptake** of 111In-DTPAOC at all time points tested, independently of the mass of 111In-DTPAOC used. Higher or repeated doses of lysine did not give a significantly higher percentage inhibition. **D-lysine**, given orally in a dose of 400 mg/kg at 30 or 15 min before 111In-DTPAOC injection, resulted in 30% and 20% inhibition of **kidney uptake**, resp. **L-lysine**, given orally 30 min before 111In-DTPAOC **administration**, resulted in 30% inhibition as well. Inhibition of **kidney uptake** of 111In-DTPAOC by **L-lysine** after i.p. **administration** was 40%. After **L-lysine administration**, 111In-DTPAOC was decreased in the kidneys and in somatostatin receptor-pos. organs such as the pancreas and adrenal glands. In contrast, **D-lysine** did not have a significant effect on uptake in octreotide receptor-pos. organs. **Renal uptake** of 90Y-DOTATOC was reduced by 65% by i.v. **D-lysine**, whereas radioactivity in blood, pancreas and adrenal glands was not affected. **D -lysine** may be preferred to **L-lysine** for redn. of **renal uptake** of radioactivity during scintigraphy and PRRT because of its lower toxicity and because it should not interfere with the natural amino acid metabolic balance.

IT **923-27-3, D-Lysine**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**D-Lysine** redn. of indium-111 octreotide and yttrium-90 octreotide **renal uptake**)

L6 ANSWER 6 OF 17 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:12681 CAPLUS
DOCUMENT NUMBER: 128:125381
TITLE: Overcoming the nephrotoxicity of radiometal-labeled immunoconjugates: improved

cancer therapy **administered** to a nude mouse model in relation to the internal radiation dosimetry

AUTHOR(S): Behr, Thomas M.; Sharkey, Robert M.; Sgouros, George; Blumenthal, Rosalyn D.; Dunn, Robert M.; Kolbert, Katherine; Griffiths, Gary L.; Siegel, Jeffry A.; Becker, Wolfgang S.; Goldenberg, David M.

CORPORATE SOURCE: Garden State Cancer Center at the Center for Molecular Medicine and Immunology, Belleville, NJ, 07109, USA

SOURCE: Cancer (N. Y.) (1997), 80(12, Suppl.), 2591-2610
CODEN: CANCAR; ISSN: 0008-543X

PUBLISHER: John Wiley & Sons, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Elevated **renal uptake** and extended **retention** of radiolabeled antibody fragments and peptides is a problem in the therapeutic application of such agents. However, cationic amino acids have been shown to reduce renal accretion. The aims of the current study were to evaluate whether this methodol. would benefit therapy with yttrium 90 (90Y)-labeled antibody fragments (Fab, F(ab)2), to establish the relationship between radiation dosimetry and obsd. biol. effects, and to compare the antitumor efficacy of antibody fragments with that of whole Ig (Ig)G. The max. tolerated dose (MTD) and the dose-limiting organ toxicity of 90Y-labeled anti-carcinoembryonic antigen (CEA) MN-14 monoclonal antibodies (Fab, F(ab)2, and IgG) were detd. in nude mice bearing GW-39 human colon carcinoma xenografts. The mice were treated with or without kidney protection by **administration** of **D-lysine**, with or without bone marrow transplantation (BMT), or with combinations of each. Toxicity and tumor growth were monitored at weekly intervals after radioimmunotherapy. Dosimetry was calcd. from bio-distribution studies using 88Y-labeled antibody. Three different dosimetric models were examd.: 1) taking solely self-to-self doses into account, using S factors for 90Y in spheroids from 0.1 to 1 g; 2) correcting for cross -organ radiation; and 3) using actual mouse anatomy as represented by NMR imaging with a three-dimensional internal dosimetry package (3D-ID). The kidney was the first dose limiting organ with the use of Fab fragments. Acute radiation nephritis occurred at injected activities .gtoreq.325 .mu.Ci, and chronic nephrosis at doses .gtoreq.250 .mu.Ci. Activities of 200 .mu.Ci were tolerated by 100% of the animals (i.e., the MTD). Application of lysine decreased the renal dose by approx. fivefold, facilitating a 25% increase in the MTD (to 250 .mu.Ci), because myelotoxicity became dose-limiting despite red marrow doses of less than 5 Gy (Gy). By using BMT and lysine, the MTD could be doubled from 200 to 400 .mu.Ci, where no biochem. or histol. evidence of

renal damage was obsd. (kidney dose, .ltoreq.40 Gy). With injected activities of .gtoreq. 325.mu.Ci without kidney protection, and with a hepatic self-to-self dose of only 4 Gy, rising liver enzymes were obsd., which could be explained only by cross-organ radiation from radioactivity in the kidneys (in the immediate neighborhood of the right kidney up to .gtoreq. 150 Gy). The MTD of F(ab)2 fragments could be elevated only by a combination of BMT and lysine. With IgG, the bone marrow alone was dose-limiting. Tumor dosimetry correlated well with antitumor effects; Fab was more effective than F(ab)2, which was consistent with its more favorable dosimetry, and it may also be more effective than IgG due to its higher dose rate and more homogenous distribution. Dosimetry Model 1 was insufficient for predicting biol. effects. Model 2 seemed to be more accurate, accounting for interorgan crossfire. However, Model 3 showed an addnl. substantial contribution to the red bone marrow dose due to crossfire from the abdominal organs. These data show that radiation nephrotoxicity is an important effect of cancer therapy with radiometal-conjugated antibody fragments or peptides. However, this effect can be overcome successfully with the application of cationic amino acids, which substantially increase the anti-tumor efficacy of radiometal-labeled immunoconjugates. For understanding the biol. effects (e.g., liver toxicity) of 90Y in a mouse model, accounting for cross-organ radiation is essential. Further studies with radiometal conjugated monoclonal antibody fragments and peptides are necessary to det. the MTD, dose-limiting organs, antitumor effectiveness, and nephroprotective effects of cationic amino acids in humans.

IT **923-27-3, D-Lysine**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(overcoming nephrotoxicity of radiometal-labeled immunoconjugates)

L6 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:722662 CAPLUS
DOCUMENT NUMBER: 128:2464
TITLE: Induction of muscle protein degradation by a tumor factor
AUTHOR(S): Lorite, M. J.; Cariuk, P.; Tisdale, M. J.
CORPORATE SOURCE: CRC Nutritional Biochemistry Research Group, Pharmaceutical Sciences Institute, Aston University, Birmingham, B4 7ET, UK
SOURCE: Br. J. Cancer (1997), 76(8), 1035-1040
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An antigen of apparent mol. wt. of 24 000, reactive with a murine monoclonal antibody, has been isolated from a cachexia-inducing

tumor (MAC 16) and has been shown to initiate muscle protein degrdn. in vitro using isolated soleus muscle. **Administration** of this material to female NMRI mice (20 g) produced a pronounced depression in body wt. (2.72 g; from control) over a 24 h period. This wt. loss was attenuated in mice pretreated with the monoclonal antibody (0.06 g over 24 h) and occurred without a redn. in food and water intake. There was no change in body water compn., and the major contribution to the decrease in body wt. was a decrease in the non-fat carcass dry wt. (mainly lean body mass). The plasma levels of glucose and most amino acids were also significantly depressed. The decrease in lean body mass was accounted for by an increase (by 50%) in protein degrdn. and a decrease (by 50%) in protein synthesis in gastrocnemius muscle. Protein degrdn. was significantly decreased and protein synthesis increased to control values in mice pretreated with the monoclonal antibody. Protein degrdn. initiated in vitro with the proteolysis-inducing factor was abolished in mice pretreated with eicosapentaenoic acid (EPA), which had been shown to prevent muscle wastage in mice bearing the MAC16 tumor. Protein degrdn. was assocd. with a significant elevation of prostaglandin E2 prodn. by isolated soleus muscle, which was inhibited by both the monoclonal antibody and EPA. These results suggest that this material may be the humoral factor mediating changes in skeletal muscle protein homeostasis during the process of cancer cachexia in animals bearing the MAC16 tumor, and could potentially be involved in other cases of cachexia.

L6 ANSWER 8 OF 17 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:561379 CAPLUS
DOCUMENT NUMBER: 127:202218
TITLE: Differential inhibitory effect of **L-lysine** on renal accumulation of 67Cu-labeled F(ab')2 fragments in mice
AUTHOR(S): Rutherford, Richard A. D.; Smith, Alan; Waibel, Robert; Schubiger, P. August
CORPORATE SOURCE: Division of Radiopharmacy, Paul Scherrer Institute, Villigen, CH-5232, Switz.
SOURCE: Int. J. Cancer (1997), 72(3), 522-529
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The basic amino acid **L-lysine** was **administered** to mice in an attempt to circumvent unwanted renal accumulation of 67Cu-labeled F(ab')2 fragments derived from the anti-NCAM IgG1, SEN7 and anti-CEA IgG1 monoclonal antibody (MAb)35. In control expts., significant **renal uptake** of both 67Cu-labeled F(ab')2 fragments was obsd., radiolabel being primarily localized to proximal tubules in the renal cortex. Following optimized **L-lysin**

dosing protocols, **renal uptake** of 67Cu-MAb35 F(ab')2 was inhibited by up to 42%. Surprisingly, little inhibition (<10%) of 67Cu-SEN7 F(ab')2 uptake was obsd. Expts. to investigate this differential inhibition indicated that inhibition of MAb35 F(ab')2 uptake was relatively short-lived (approx. 6 h), while no apparent differences were found in blood clearance rates between either 67Cu-F(ab')2 fragment. **L-Lysine administration** caused a significant diuresis with high levels of intact 67Cu-labeled SEN7 and MAb35 F(ab')2 appearing in the urine, possibly due to blockade of **renal uptake** and lysine-induced increases in glomerular membrane permeability. Isoelec. focusing studies failed to identify any charge differences between the 67Cu-labeled F(ab')2 fragments, although a cathodal migration of all 67Cu-labeled samples, presumably due to the net pos. charge conferred by addn. of 67Cu2+ ions, was obsd. Our results demonstrate that in addn. to net charge, other unidentified characteristics may influence renal accumulation of radiometal-labeled F(ab')2 fragments and their inhibition by **L-lysine**.

L6 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:681542 CAPLUS
DOCUMENT NUMBER: 125:317395
TITLE: Lysine and polylysine for reduced **renal uptake** of antibody fragments
INVENTOR(S): Behr, Thomas M.; Goldenberg, David M.
PATENT ASSIGNEE(S): Center for Molecular Medicine and Immunology, USA
SOURCE: PCT Int. Appl., 37 pp
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9629087	A1	19960926	WO 1996-US3308	19960320
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML				
US 5843894	A	19981201	US 1995-407899	19950321
CA 2190867	AA	19960926	CA 1996-2190867	19960320
AU 9653616	A1	19961008	AU 1996-53616	19960320
AU 700346	B2	19990107		

Searcher : Shears 308-4994

EP 767673	A1	19970416	EP 1996-910422	19960320
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 10505866	T2	19980609	JP 1996-528465	19960320
PRIORITY APPLN. INFO.:			US 1995-407899	19950321
			WO 1996-US3308	19960320

AB **Kidney uptake** of antibody fragment conjugates in patients undergoing radioimmunodiagnosis, immunotherapy, or radioimmunotherapy is reduced by **administration** of the patient of one or more compds. selected from the group consisting of lysine and/or polylysine, pharmaceutically acceptable salts or carboxyl derivs. thereof. Human patients undergoing radioimmunodetection with 99mTc-labeled Fab' fragments of two anti-carcinoembryonic antigen antibodies were infused over a 3-h period with a com. amino acid soln. contg. 1.75 g **L-lysine**. A decrease of **kidney uptake** of radiolabeled fragments was obsd., the effect being more pronounced at 24 h than at 4 h post injection. However, poly(**L-lysine**) with a mol. wt. of 1-4 kDa reduced **kidney uptake** with a single i.p. injection at lower doses than the monomer. The potency of poly(**L-lysine**) increased with increasing mol. wt.

IT **923-27-3**, **D-Lysine 25104-18-1**, Poly(**L-lysine**) **38000-06-5**, Poly(**L-lysine**)
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lysine and/or polylysine for reduced **renal uptake** of antibody fragments in radioimmunodiagnosis and (radio)immunotherapy)

L6 ANSWER 10 OF 17 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER:	1996:621182 CAPLUS
DOCUMENT NUMBER:	125:293629
TITLE:	Influence of triiodothyronine and dexamethasone on renal amino acid handling in rats loaded with various amino acid mixtures
AUTHOR(S):	Fleck, C.; Nussbaum, R. P.
CORPORATE SOURCE:	Inst. Pharmacology Toxicology, Friedrich-Schiller-Univ., Jena, D-07740, Germany
SOURCE:	Amino Acids (1996), 11(1), 55-68 CODEN: AACIE6; ISSN: 0939-4451
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB In adult female rats, the influence of dexamethasone (D) or triiodothyronine on renal amino acid handling was investigated in amino acid loaded animals. Amino acids were **administered** i.v. as 2 mixts. each contg. 4 amino acids to overload amino acid reabsorption capacity. Bolus injections of both mixts. were

followed by temporary increase in fractional excretion of the **administered** amino acids as well of amino acids which were not covered in the mixts. Triiodothyronine (20 .mu.g/100 g for 3 days, once daily) did not increase tubular reabsorption capacity for amino acids. The **administration** of the 2 mixts. was followed by different interactions between various amino acid carriers. After D pretreatment (60 .mu.g/100 g for 3 days, once daily) a stimulation of the renal amino acid handling could be shown. It even increased fractional amino acid excretion in amino acid loaded rats as a sign of enhanced amino acid metab. in the **kidney** and/or increased amino acid **uptake** into the tubular cells from the luminal site.

L6 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:506724 CAPLUS
DOCUMENT NUMBER: 125:189588
TITLE: **L-Lysine** effectively blocks **renal uptake** of 125I- or 99mTc-labeled anti-Tac disulfide-stabilized Fv fragment
AUTHOR(S): Kobayashi, Hisataka; Yoo, Tae M.; Kim, In S.; Kim, Meyoung-Kon; Keith, Nhat Le; Webber, Keith O.; Pastan, Ira; Paik, Chang H.; Eckelman, William C.; Carrasquillo, Jorge A.
CORPORATE SOURCE: Dep. Nuclear Med., Positron Emission Tomography Dep., Bethesda, MD, 20892-1180, USA
SOURCE: Cancer Res. (1996), 56(16), 3788-3795
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In this study, we investigated the ability of **L-lysine** to block **renal uptake** of 125I- or 99mTc-labeled Fv fragments. Anti-Tac disulfide-stabilized Fv fragment (dsFv) was derived from a murine monoclonal antibody that recognizes the .alpha. subunit of the interleukin-2 receptor (IL-2R.alpha.). The 125I- or 99mTc-labeled dsFv was injected i.v. into non-tumor-bearing nude mice or into nude mice bearing SP2/Tac (IL-2R.alpha. pos.) and SP2/0 (IL-2R.alpha. neg.) tumor. We then evaluated the pharmacokinetics of L-[3H]lysine and the effect of **L-lysine** dose, timing of **administration**, and route of delivery on catabolism and biodistribution of i.v. dsFv. Peak **renal uptake** of i.v. or i.p. injected L-[3H]lysine occurred within 5 and 15 min, resp. The **kidney uptake** of **L-lysine** exhibited a dose-response effect. When **L-lysine** was coinfused or injected shortly before dsFv, **renal uptake** of dsFv was blocked to <5% of the control, but longer intervals were less effective. Aminosyn II and Travasol 10% (parenteral amino acid solns.) also blocked **renal**

uptake of radiolabeled dsFv. **Administration** of **L-lysine** did not alter the blood kinetics and slightly increased the tumor uptake of dsFv, but it did prevent catabolism in the kidney and resulted in lower amts. of catabolites in the serum and urine. In conclusion, we have shown that a blocking dose of lysine, injected with or immediately before the injection of radiolabeled dsFv, is most effective in blocking the **renal uptake** of dsFv. This is consistent with the rapid uptake of L-[3H]lysine by the kidney and is further substantiated by the relative ineffectiveness of lysine injected immediately after the radiolabeled dsFv injection.

L6 ANSWER 12 OF 17 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:274682 CAPLUS
DOCUMENT NUMBER: 122:52240
TITLE: Reabsorption of proteins in renal tubules
AUTHOR(S): Kudo, Shoji; Goto, Hirohiko; Odomi, Masaaki
CORPORATE SOURCE: Tokushima Research Institute, Otsuka Pharmaceutical Co., Ltd., Tokushima, 771-01, Japan
SOURCE: Yakubutsu Dotai (1994), 9(Suppl.), S114-S117
CODEN: YADOEL; ISSN: 0916-1139
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB To investigate the mechanism of the resorption of a protein in renal tubules of rats, the authors employed OCT-7000, which is a recombinant variant of natural human interleukin-1.alpha. with a mol. mass of approx. 18,000. In this study, OCT-7000 **uptake** in **renal** tubules was examd. using immunoelectron microscopic technique with immunogold staining. The effects of various proteins or synthetic polypeptides on the urinary excretion of OCT-7000 were also investigated. Immunoelectron microscopic observations showed that OCT-7000 was taken up into the endocytic vesicle close to the brush border membrane located in segment 2 of the proximal tubules, followed by accumulation of secondary lysosomes. Urinary excretion of OCT-7000 after systemic **administration** was extremely low, accounting for 0.014% of the dose. Human serum albumin had no effect on the excretion of OCT-7000, while increases in the urinary excretion of OCT-7000 were found in rats treated with a trypsin inhibitor, myoglobin and trypsinogen, in a dose-dependent manner. The order of potency for urinary excretion of OCT-7000 was trypsinogen > myoglobin > trypsin inhibitor. Poly-**L-lysine**, a synthetic polypeptide dose-dependently increased the urinary excretion of OCT-7000, whereas poly-L-glutamic acid had no effect on excretion. Specifically, the data reveal that resorption of OCT-7000 in the proximal tubules was inhibited by trypsinogen, myoglobin, trypsin inhibitor or poly-**L-lysine**, resulting in an increase of urinary excretion of OCT-7000. Furthermore, it was

considered that neg. charges on the brush border membrane in the proximal tubules were involved in the resorption of OCT-7000 because the inhibitory potency of proteins or synthetic polypeptides on the resorption of OCT-7000 was increased with a high isoelec. point. The mechanisms of resorption of protein in renal tubule are discussed.

IT **25104-18-1**, Poly-**L-lysine**
38000-06-5, Poly-**L-lysine**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(reabsorption of proteins in renal tubules in response to)

L6 ANSWER 13 OF 17 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1993:87490 CAPLUS
DOCUMENT NUMBER: 118:87490
TITLE: Copolymers of lysine and polyethylene glycol: a new family of functionalized drug carriers
AUTHOR(S): Nathan, Aruna; Zalipsky, Samuel; Ertel, Sylvie I.; Agathos, Spiro N.; Yarmush, Martin L.; Kohn, Joachim
CORPORATE SOURCE: Dep. Chem., Rutgers-State Univ., New Brunswick, NJ, 08903, USA
SOURCE: Bioconjugate Chem. (1993), 4(1), 54-62
CODEN: BCCHES; ISSN: 1043-1802
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Poly(PEG-Lys), a new, water-sol. poly(ether urethane), derived from **L-lysine** and poly(ethylene glycol) was investigated as a precursor for the prepn. of polymeric drug conjugates. To facilitate a wide variety of coupling chemistries, the pendent carboxyl groups of poly(PEG-Lys) were converted to other reactive functional groups (amino, hydroxyl, active ester, and aldehyde) in high yield. These reactive pendent chains were than used as anchors for the covalent attachment of penicillin V and cephradine, two clin. used antimicrobial agents. Coupling to the carrier was achieved in good yields and the chem. versatility of this system was demonstrated by the prepn. of conjugates having antibiotic ligands linked via biostable or biodegradable linkages to the carrier, either directly or via a spacer. A conjugate, poly(PEG-Lys-penicillin V ester), was obtained by linking penicillin V to the polymer backbone via hydrolytically labile ester bonds. This conjugate exhibited activity similar to that of the parent drug against three clin. important strains of bacteria. Drug activity coincided with the release of the drug from the carrier. Hydrolytically stable cephradine-contg. conjugates were prepd. by three different coupling methods but showed no antibiotic activity. 14C-labeled poly(PEG-Lys) was injected into mice and its biodistribution was monitored for 48 h. The carrier showed no preferential **uptake** by liver, spleen, or **kidney**.

No signs of acute toxicity were evident in mice or rats when poly(PEG-Lys) was **administered** i.v. and i.p. at doses up to 10 g/kg. These results indicate that poly(PEG-Lys) is a promising precursor for the prepn. of sol. drug conjugates.

L6 ANSWER 14 OF 17 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1990:637684 CAPLUS
DOCUMENT NUMBER: 113:237684
TITLE: Pharmacokinetics of methotrexate after intramuscular injection of methotrexate-polylysine conjugate in rabbits
AUTHOR(S): Yoon, Eun Jeong; Lee, Myung Gull; Lee, Hee Joo; Park, Man Ki; Kim, Chong Kook
CORPORATE SOURCE: Coll. Pharm., Seoul Natl. Univ., Seoul, 151-742, S. Korea
SOURCE: Arch. Pharmacal Res. (1990), 13(2), 147-50
CODEN: APHRDQ; ISSN: 0253-6269
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Methotrexate (MTX)-poly(**L-lysine**)(PLL) conjugate was relatively stable in phosphate buffer of pH 7.4 and in plasma. However, liver homogenate accelerated the release of MTX from the conjugate. Pharmacokinetics and tissue distribution of MTX were compared after i.m. injection of MTX (treatment I) and MTX-PLL conjugate (treatment II), 10 mg/kg as free MTX to rabbits. The peak concns. of MTX in treatment II were lower than those in treatment I. The amt. of MTX excreted in 24-h urine was reduced in treatment II and is suggested that MTX be more metabolized in treatment II than in treatment I. The amts. of MTX remaining in each organ after 24-h of i.m. injection were not different in both treatments.
IT **25104-18-1D**, Poly(**L-lysine**), conjugates with methotrexate **38000-06-5D**, Poly(**L-lysine**), conjugates with methotrexate
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(pharmacokinetics of, i.v. **administration** of free drug in relation to)

L6 ANSWER 15 OF 17 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1985:106310 CAPLUS
DOCUMENT NUMBER: 102:106310
TITLE: Nephrotoxicity inhibitors for aminoglycoside antibiotics
INVENTOR(S): Williams, Patricia D.; Hottendorf, Girard H.
PATENT ASSIGNEE(S): Bristol-Myers Co. , USA
SOURCE: Brit. UK Pat. Appl., 14 pp.
CODEN: BAXXDU
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 2139087	A1	19841107	GB 1984-10804	19840427
GB 2139087	B2	19870325		
US 4526888	A	19850702	US 1983-489999	19830429
NL 8401322	A	19841116	NL 1984-1322	19840425
ZA 8403075	A	19841224	ZA 1984-3075	19840425
JP 59206311	A2	19841122	JP 1984-83039	19840426
JP 05053776	B4	19930810		
BE 899542	A1	19841029	BE 1984-212851	19840427
SE 8402333	A	19841030	SE 1984-2333	19840427
SE 466288	B	19920127		
SE 466288	C	19920527		
AU 8427442	A1	19841101	AU 1984-27442	19840427
AU 560158	B2	19870402		
FR 2544986	A1	19841102	FR 1984-6741	19840427
FR 2544986	B1	19870619		
DE 3415805	A1	19850228	DE 1984-3415805	19840427
CH 660457	A	19870430	CH 1984-2088	19840427
CA 1227135	A1	19870922	CA 1984-452933	19840427
PRIORITY APPLN. INFO.:			US 1983-489999	19830429

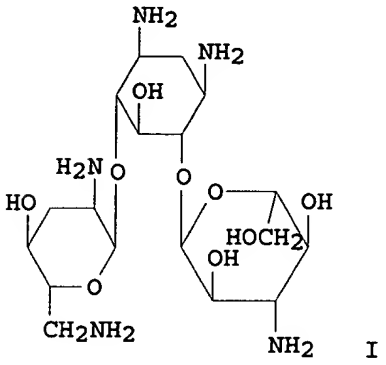
AB Polymers of asparagine, e.g. poly-L-asparagine (PAsp) [28088-48-4] and of aspartic acid, e.g. poly-L-aspartic acid (PAA) [25608-40-6] or their copolymer [95144-25-5] when **administered** cojointly with an aminoglycoside antibiotic, reduced the nephrotoxicity of the antibiotic apparently by inhibiting the **renal uptake** or binding of the aminoglycoside. Thus, the gentamicin-PAsp mixt. [95148-96-2] or the amikacin-PAA mixt. [95149-05-6] had decreased nephrotoxicity when compared to that obsd. in rats treated with gentamicin [1403-66-3] or amikacin [37517-28-5], resp.

IT **25104-18-1 38000-06-5**
RL: BIOL (Biological study)
(aminoglycoside antibiotic membrane transport response to, nephrotoxicity in relation to)

L6 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1982:484637 CAPLUS
DOCUMENT NUMBER: 97:84637
TITLE: Modulation of **renal** cortical aminoglycoside **uptake** by concurrent amino acid **administration**
AUTHOR(S): Whelton, A.; Stout, R. L.; Carter, G. G.; Craig, T. J.; Bryant, H. H.; Herbst, D. V.; Walker, W. G.
CORPORATE SOURCE: Sch. Med., Johns Hopkins Univ., Baltimore, MD,

Searcher : Shears 308-4994

USA
SOURCE: Colloq. - Inst. Natl. Sante Rech. Med. (1982), 102(Nephrotoxic.: Ototoxic. Med.), 39-54
CODEN: CINMDE
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The effect of amino acids on the **renal** cortical **uptake** of aminoglycosides, tobramycin (I) [32986-56-4] and gentamicin (II) [1403-66-3], was studied in dogs. Both **administration** of a mixt. of amino acids (FreAmine II) and **administration** of **L-lysine** [56-87-1] (which can sat. and block reabsortion of basically charged amino acids) decreased the renal cortical concns. of I and II. However, satn. of either the acid or the neutral amino acid pathways of renal tubular transport with L-glutamic acid [56-86-0] and glycine [56-40-6], resp., did not influence renal cortical accumulation of I or II. Satn. of proximal tubular glucose [50-99-7] reabsorption did not concomitantly influence renal cortical II accumulation. Further, **D-lysine** [923-27-3], an amino acid which is not or very minimally transported by the renal proximal tubules decreased II **renal** cortical **uptake**. Both the possible mechanisms and the clin. implications of the results are discussed.

IT **923-27-3**
RL: BIOL (Biological study)
(**kidney uptake** of aminoglycoside antibiotic modulation with)

L6 ANSWER 17 OF 17 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1973:69839 CAPLUS
DOCUMENT NUMBER: 78:69839
TITLE: Cellular accumulation of L-cystine in rat kidney

cortex in vivo

AUTHOR(S): Greth, Warren E.; Thier, Samuel O.; Segal, Stanton

CORPORATE SOURCE: Div. Biochem. Dev. Mol. Dis., Child. Hosp., Philadelphia, Pa., USA

SOURCE: J. Clin. Invest. (1973), 52(2), 454-62
CODEN: JCINAO

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Cellular accumulation of L-cystine in rat kidney cortex in vivo has been studied using L-[35S]-cystine. The L-[35S]-cystine radioactivity in plasma decreases to less than 10% of the initially calcd. value by 15 min. Four 35S-contg. intracellular products of L-cystine metab. were identified, including cystine, cysteine, reduced glutathione, and an unidentified compd. The latter is probably taurine, cysteinesulfinate, or cysteic acid. Cellular accumulation of these products was more rapid in vivo than in vitro. Cellular accumulation of the products of L-cystine metab. was essentially unchanged in the presence of ureter ligation. Unlabeled **L-lysine administered** simultaneously with L-[35S]-cystine, in both the presence and absence of ureter ligation, enhanced the cellular accumulation of intracellular metabolic products of L-[35S]-cystine. Simultaneous 35S cellular accumulation and L-cystine clearance studies were performed both in the presence and absence of **L-lysine**. **L-Lysine** enhanced cellular accumulation of 35S products despite an accompanying increase in L-cystine clearance. The results are interpreted as evidence for a dissocn. between cellular accumulation and transepithelial transport. This evidence for independent luminal transport and peritubular cellular accumulation could explain the apparent paradox in the disease cystinuria where there appears to be a luminal transport defect for L-cystine, but no defect for cellular accumulation of L-cystine metabolic products in vitro.

FILE 'REGISTRY' ENTERED AT 10:04:31 ON 09 MAY 2000
D SAV
ACT BURKE2007/A

L1 (1) SEA ABB=ON PLU=ON D-LYSINE/CN
L2 (2) SEA ABB=ON PLU=ON POLY-L-LYSINE/CN
L3 3 SEA ABB=ON PLU=ON L1 OR L2

FILE 'CAPLUS' ENTERED AT 10:04:49 ON 09 MAY 2000
ACT BURKE200/A

L4 (1) SEA ABB=ON PLU=ON D-LYSINE/CN
L5 (2) SEA ABB=ON PLU=ON POLY-L-LYSINE/CN

Searcher : Shears 308-4994

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L6   (         3)SEA ABB=ON  PLU=ON  L4 OR L5
L7   (     20986)SEA ABB=ON  PLU=ON  L6 OR (L OR D)(W)(LYSINE OR LYS)
L8   (        51)SEA ABB=ON  PLU=ON  L7 AND (KIDNEY OR RENAL?)(5A)(UPTAK?
                   OR RETEN?)
L9            17 SEA ABB=ON  PLU=ON  L8 AND ADMIN?
                 ---------

     FILE 'MEDLINE, BIOSIS, EMBASE, LIFESCI, WPIDS, CONFSCI, SCISEARCH,
     JICST-EPLUS' ENTERED AT 10:05:47 ON 09 MAY 2000
L10           47 SEA ABB=ON  PLU=ON  L9
L11           19 DUP REM L10 (28 DUPLICATES REMOVED)

L11  ANSWER 1 OF 19  MEDLINE                              DUPLICATE 1
ACCESSION NUMBER:    1999221136     MEDLINE
DOCUMENT NUMBER:     99221136
TITLE:               A novel immunoscintigraphy technique using
                     metabolizable linker with angiotensin II treatment.
AUTHOR:              Nakamoto Y; Sakahara H; Saga T; Sato N; Zhao S; Arano
                     Y; Fujioka Y; Saji H; Konishi J
CORPORATE SOURCE:    Department of Nuclear Medicine and Diagnostic
                     Imaging, Graduate School of Medicine, Kyoto
                     University Hospital, Japan.
SOURCE:              BRITISH JOURNAL OF CANCER, (1999 Apr) 79 (11-12)
                     1794-9.
                     Journal code: AV4. ISSN: 0007-0920.
PUB. COUNTRY:        SCOTLAND: United Kingdom
                     Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals; Cancer Journals
ENTRY MONTH:         199907
ENTRY WEEK:          19990702
AB   Immunoscintigraphy is a tumour imaging technique that can have
     specificity, but high background radioactivity makes it difficult to
     obtain tumour imaging soon after the injection of radioconjugate.
     The aim of this study is to see whether clear tumour images can be
     obtained soon after injection of a radiolabelled reagent using a new
     linker with antibody fragments (Fab), in conditions of induced
     hypertension in mice. Fab fragments of a murine monoclonal antibody
     against human osteosarcoma were labelled with radioiodinated
     3'-iodohippuryl N-epsilon-maleoyl-L-lysine (HML)
     and were injected intravenously to tumour-bearing mice. Angiotensin
     II was administered for 4 h before and for 1 h after the
     injection of radiolabelled Fab. Kidney uptake of
     125I-labelled-HML-Fab was much lower than that of 125I-labelled-Fab
     radioiodinated by the chloramine-T method, and the radioactivity of
     tumour was increased approximately two-fold by angiotensin II
     treatment at 3 h after injection, indicating high tumour-to-normal
     tissue ratios. A clear tumour image was obtained with
     131I-labelled-HML-Fab at 3 h post-injection. The use of HML as a
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radiolabelling reagent, combined with angiotensin II treatment, efficiently improved tumour targeting and enabled the imaging of tumours. These results suggest the feasibility of PET scan using antibody fragment labelled with 18F-fluorine substitute for radioiodine.

L11 ANSWER 2 OF 19 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1999216402 MEDLINE
DOCUMENT NUMBER: 99216402
TITLE: Uptake kinetics of the somatostatin receptor ligand [86Y]DOTA-DPhe1- Tyr3-octreotide ([86Y]SMT487) using positron emission tomography in non-human primates and calculation of radiation doses of the 90Y-labelled analogue.
AUTHOR: Rosch F; Herzog H; Stolz B; Brockmann J; Kohle M; Muhlensiepen H; Marbach P; Muller-Gartner H W
CORPORATE SOURCE: Institut fur Nuklearchemie, Forschungszentrum Julich, Germany.
SOURCE: EUROPEAN JOURNAL OF NUCLEAR MEDICINE, (1999 Apr) 26 (4) 358-66.
Journal code: ENC. ISSN: 0340-6997.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY WEEK: 19990801

AB [90Y]DOTA-DPhe1-Tyr3-octreotide ([90Y]-SMT487) has been suggested as a promising radiotherapeutic agent for somatostatin receptor-expressing tumours. In order to quantify the in vivo parameters of this compound and the radiation doses delivered to healthy organs, the analogue [86Y]DOTA-DPhe1-Tyr3-octreotide was synthesised and its uptake measured in baboons using positron emission tomography (PET). [86Y]DOTA-DPhe1-Tyr3-octreotide was **administered** at two different peptide concentrations, namely 2 and 100 microg peptide per m2 body surface. The latter concentration corresponded to a radiotherapeutic dose. In a third protocol [86Y]DOTA-DPhe1-Tyr3-octreotide was injected in conjunction with a simultaneous infusion of an amino acid solution that was high in **l-lysine** in order to lower the **renal uptake** of radioyttrium. Quantitative whole-body PET scans were recorded to measure the **uptake** kinetics for **kidneys**, liver, lung and bone. The individual absolute uptake kinetics were used to calculate the radiation doses for [90Y]DOTA-DPhe1-Tyr3-octreotide according to the MIRD recommendations extrapolated to a 70-kg human. The highest radiation dose was received by the kidneys, with 2.1-3.3 mGy per MBq [90Y]DOTA-DPhe1-Tyr3-octreotide injected. For the 100 microg/m2 SMT487 protocol with amino acid co-infusion this dose was about

20%-40% lower than for the other two treatment protocols. The liver and the red bone marrow received doses ranging from 0.32 to 0.53 mGy and 0.03 to 0.07 mGy per MBq [90Y]DOTA-DPhe1-Tyr3-octreotide, respectively. The average effective dose equivalent amounted to 0.23-0.32 mSv/MBq. The comparatively low estimated radiation doses to normal organs support the initiation of clinical phase I trials with [90Y]DOTA-DPhe1-Tyr3-octreotide in patients with somatostatin receptor-expressing tumours.

L11 ANSWER 3 OF 19 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1999107215 MEDLINE
DOCUMENT NUMBER: 99107215
TITLE: Chemical design of radiolabeled antibody fragments for low renal radioactivity levels.
AUTHOR: Arano Y; Fujioka Y; Akizawa H; Ono M; Uehara T; Wakisaka K; Nakayama M; Sakahara H; Konishi J; Saji H
CORPORATE SOURCE: Department of Patho-Functional Bioanalysis, Graduate School of Pharmaceutical Sciences, Kyoto University, Japan.. arano@pharm.kyoto-u.ac.jp
SOURCE: CANCER RESEARCH, (1999 Jan 1) 59 (1) 128-34. Journal code: CNF. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199904
ENTRY WEEK: 19990401

AB The **renal uptake** of radiolabeled antibody fragments presents a problem in targeted imaging and therapy. We hypothesized that the renal radioactivity levels of radiolabeled antibody fragments could be reduced if radiolabeled compounds of urinary excretion were released from glomerularly filtered antibody fragments before they were incorporated into renal cells by the action of brush border enzymes, present on the lumen of renal tubules. 3'-[131I]Iodohippuryl N(epsilon)-maleoyl-**L-lysine** ([131I]HML) was conjugated with a thiolated Fab fragment because the glycyl-lysine sequence in HML is a substrate for a brush border enzyme and metaiodohippuric acid is released by cleavage of the linkage. Fab fragments were also radiolabeled by direct radioiodination (125I-Fab) or by conjugation with meta-[125I]-iodohippuric acid via an amide bond [N-(5-maleimidopentyl) 3'-iodohippuric acid amide ([125I]MPH-Fab)] or an ester bond [maleimidoethy 3'-iodohippurate ([125I]MIH-Fab)] by procedures similar to those used for [131I]HML-Fab. In biodistribution experiments in mice, [131I]HML-Fab demonstrated markedly low renal radioactivity levels with kidney:blood ratios of radioactivity of 1 from 10 min to 1 h due to rapid release of meta-[131I]iodohippuric acid. [125]MIH-Fab and 1251-Fab reached their peak ratios of 3.8 and 7.3 at 1 h, respectively, and

[125I]MPH-Fab showed the maximum ratio of 16.8 at 6 h. In subcellular distribution studies, both [125I]MIH-Fab and 125I-Fab showed migration of radioactivity from the membrane to the lysosomal fraction of the renal cells from 10 to 30 min postinjection, whereas the majority of the radioactivity was detected only in the membrane fraction after **administration** of [131I]HML-Fab at both time points. In nude mice, [131I]HML-Fab showed one-quarter of the renal radioactivity of simultaneously **administered** 125I-Fab without impairing the target radioactivity levels 3 h after injection. These findings indicated that HML is a useful reagent for targeted imaging and therapy using antibody fragments as vehicles. These findings also suggested that the radiochemical design of radiolabeled antibody fragments that liberate radiometabolites of urinary excretion from antibody fragments by the action of brush border enzymes may constitute a new strategy for reducing the renal radioactivity levels of antibody fragments.

L11 ANSWER 4 OF 19 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1999034520 MEDLINE
DOCUMENT NUMBER: 99034520
TITLE: 90Yttrium-labeled complementarity-determining-region-grafted monoclonal antibodies for radioimmunotherapy: radiolabeling and animal biodistribution studies.
AUTHOR: Govindan S V; Shih L B; Goldenberg D M; Sharkey R M; Karacay H; Donnelly J E; Losman M J; Hansen H J; Griffiths G L
CORPORATE SOURCE: Immunomedics, Inc., 300 American Road, Morris Plains, New Jersey 07950, and Garden State Cancer Center, Belleville, New Jersey 07109, USA.
CONTRACT NUMBER: CA 39841 (NCI)
CA 66348 (NCI)
SOURCE: BIOCONJUGATE CHEMISTRY, (1998 Nov-Dec) 9 (6) 773-82. Journal code: A1T. ISSN: 1043-1802.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
AB 90Yttrium-labeled monoclonal antibodies (mAbs) are likely to be important to radioimmunotherapy (RAIT) of a variety of cancers. The goal of this study was to select and evaluate a form of [90Y]mAb suitable for RAIT and determine conditions for high-yield, reproducible radiolabelings. 90Y-Labelings, at 2-40 mCi levels, of cdr-grafted versions of anti-B-cell lymphoma (hLL2) and anti-CEA (hIMMU-14) mAbs were optimized to >90% incorporations using the macrocyclic chelator DOTA as the metal carrier. In in vitro challenge assays, the stability of mAbs labeled with [90Y]DOTA was better than that of the corresponding [90Y]benzyl-DTPA conjugates. The retention of [90Y]DOTA-hLL2 on Raji tumor cells in vitro was

similar to that of the same mAb labeled with [90Y]benzyl-DTPA and was about twice as much as with [125I]hLL2, indicating residualization of metalated mAb. Both [90Y]hLL2 conjugates, prepared using DOTA and Bz-DTPA, had similar maximum tolerated doses of 125 muCi in BALB/c mice and showed no discernible chelator-induced immune responses. Animal biodistribution studies in nude mice bearing Ramos human B-cell lymphoma xenografts revealed similar tumor and tissue uptake over a 10 day period, with the exception of bone uptake which was up to 50% lower for [88Y]DOTA-hLL2 compared to [88Y]Bz-DTPA-hLL2 at time points beyond 24 h. With [90Y]DOTA-hLL2 fragments, in vivo animal tumor dosimetries were inferior to those for the IgG, and **kidney uptake** was relatively high even with **D-lysine administration**. The ability of [111In]DOTA-hLL2 to accurately predict [90Y]DOTA-hLL2 biodistribution was established. These preclinical findings demonstrate that [90Y]DOTA-(CDR-grafted) mAbs are suitable for examination in clinical RAIT.

L11 ANSWER 5 OF 19 MEDLINE
ACCESSION NUMBER: 1998115337 MEDLINE
DOCUMENT NUMBER: 98115337
TITLE: Pre-clinical comparison of [DTPA0] octreotide, [DTPA0,Tyr3] octreotide and [DOTA0,Tyr3] octreotide as carriers for somatostatin receptor-targeted scintigraphy and radionuclide therapy.
AUTHOR: De Jong M; Bakker W H; Breeman W A; Bernard B F; Hofland L J; Visser T J; Srinivasan A; Schmidt M; Behe M; Macke H R; Krenning E P
CORPORATE SOURCE: Department of Nuclear Medicine, University Hospital Dijkzigt, Rotterdam, The Netherlands.. dejong@nuge.azr.nl
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1998 Jan 30) 75 (3) 406-11.
Journal code: GQU. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199804
AB We have evaluated the potential usefulness of radiolabelled [DTPA0,Tyr3]octreotide and [DOTA0,Tyr3]octreotide as radiopharmaceuticals for somatostatin receptor-targeted scintigraphy and radiotherapy. In vitro somatostatin receptor binding and in vivo metabolism in rats of the compounds were investigated in comparison with [111In-DTPA0] octreotide. Comparing different peptide-chelator constructs, [DTPA0,Tyr3]octreotide and [DOTA0,Tyr3]octreotide were found to have a higher affinity than [DTPA0]octreotide for subtype 2 somatostatin receptors (sst2) in mouse AtT20 pituitary tumour cell

membranes (all IC50 values obtained were in the low nanomolar range). In vivo studies in CA20948 tumor-bearing Lewis rats revealed a significantly higher uptake of both 111In-labelled [DOTA0,Tyr3]octreotide and [DTPA0,Tyr3]octreotide in sst2-expressing tissues than after injection of [111In-DTPA0]octreotide, showing that substitution of Tyr for Phe at position 3 in octreotide results in an increased affinity for its receptor and in a higher target tissue uptake. Uptake of 111In-labelled [DTPA0]octreotide, [DTPA0,Tyr3]octreotide and [DOTA0,Tyr3]octreotide in pituitary, pancreas, adrenals and tumour was decreased to less than 7% of control by pre-treatment with 0.5 mg unlabelled octreotide/rat, indicating specific binding to sst2. Comparing different radionuclides, [90Y-DOTA0,Tyr3]octreotide had the highest uptake in sst2-positive organs, followed by the [111In-DOTA0,Tyr3]octreotide, whereas [DOTA0,125I-Try3]octreotide uptake was low compared to that of the other radiopharmaceuticals, when measured 24 hr after injection. **Renal uptake** of 111In-labelled [DTPA0]octreotide, [DTPA0,Tyr3]octreotide and [DOTA0,Tyr3]octreotide was reduced over 50% by an i.v. injection of 400 mg/kg **D-lysine**, whereas radioactivity in blood, pancreas and adrenals was not affected.

L11 ANSWER 6 OF 19 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1998244891 MEDLINE
DOCUMENT NUMBER: 98244891
TITLE: Streptavidin in antibody pretargeting. 2. Evaluation Of methods for decreasing localization of streptavidin to kidney while retaining its tumor binding capacity.
AUTHOR: Wilbur D S; Hamlin D K; Buhler K R; Pathare P M; Vessella R L; Stayton P S; To R
CORPORATE SOURCE: Departments of Radiation Oncology, Urology, and Bioengineering, University of Washington, Seattle USA.. dswilbur@u.washington.edu
SOURCE: BIOCONJUGATE CHEMISTRY, (1998 May-Jun) 9 (3) 322-30. Journal code: A1T. ISSN: 1043-1802.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY WEEK: 19980901
AB An investigation has been conducted to determine if the kidney localization of recombinant streptavidin can be decreased to improve its characteristics in pretargeting protocols. Three different methods of accomplishing this were evaluated. The first method, blocking **kidney uptake** with a preadministration of recombinant streptavidin in which biotin occupied all of the binding sites, was unsuccessful. In a second method, 1-

lysine administration was used to block kidney localization. This method worked well, decreasing the concentration to 29% of the unmodified amount at 8 h postinjection. However, this method suffered from a requirement for constant infusion of lysine during the period of observation. A third method, use of succinylated recombinant streptavidin, was found to be the best approach. Succinylation of streptavidin was readily accomplished with very good protein recovery. With the succinylated streptavidin, the kidney concentration was only 14% of that of nonmodified streptavidin at 4 h postinjection. While these results demonstrated that the concentration of streptavidin could be decreased in the kidney, it was important to assess whether the tumor colocalization of streptavidin with biotinylated antibody was affected under those conditions. As part of our continuing investigation of pretargeting, a new water-solubilized biotinidase-stabilized biotinylation reagent was prepared. Using that reagent in a pretargeting experiment, an equivalent quantity of succinylated recombinant streptavidin as biotinylated antibody Fab' was localized in a tumor xenograft model. In that experiment, the kidney concentration was decreased to less than 10% of that obtained with unmodified recombinant streptavidin at 24 h postinjection. The results of our investigation have demonstrated that succinylation of streptavidin improves its distribution characteristics for pretargeting applications. The fact that succinylated streptavidin has no specific tissue localization should allow its use as a carrier of radioactivity in "two-step" pretargeting protocols.

L11 ANSWER 7 OF 19 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 1998068549 MEDLINE
DOCUMENT NUMBER: 98068549
TITLE: Overcoming the nephrotoxicity of radiometal-labeled immunoconjugates: improved cancer therapy **administered** to a nude mouse model in relation to the internal radiation dosimetry.
AUTHOR: Behr T M; Sharkey R M; Sgouros G; Blumenthal R D; Dunn R M; Kolbert K; Griffiths G L; Siegel J A; Becker W S; Goldenberg D M
CORPORATE SOURCE: Garden State Cancer Center at the Center for Molecular Medicine and Immunology, Belleville, New Jersey, USA.
CONTRACT NUMBER: CA39841 (NCI)
CA62444 (NCI)
SOURCE: CANCER, (1997 Dec 15) 80 (12 Suppl) 2591-610.
Journal code: CLZ. ISSN: 0008-543X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
Searcher : Shears 308-4994

ENTRY MONTH: 199803
ENTRY WEEK: 19980302

AB BACKGROUND: Elevated **renal uptake** and extended **retention** of radiolabeled antibody fragments and peptides is a problem in the therapeutic application of such agents. However, cationic amino acids have been shown to reduce renal accretion. The aims of the current study were to evaluate whether this methodology would benefit therapy with yttrium 90 (90Y)-labeled antibody fragments (Fab, F(ab)2), to establish the relationship between radiation dosimetry and observed biologic effects, and to compare the antitumor efficacy of antibody fragments with that of whole immunoglobulin (Ig)G. METHODS: The maximum tolerated dose (MTD) and the dose-limiting organ toxicity of 90Y-labeled anti-carcinoembryonic antigen (CEA) MN-14 monoclonal antibodies (Fab, F(ab)2, and IgG) were determined in nude mice bearing GW-39 human colon carcinoma xenografts. The mice were treated with or without kidney protection by **administration** of **D-lysine**, with or without bone marrow transplantation (BMT), or with combinations of each. Toxicity and tumor growth were monitored at weekly intervals after radioimmunotherapy. Dosimetry was calculated from biodistribution studies using 88Y-labeled antibody. Three different dosimetric models were examined: 1) taking solely self-to-self doses into account, using S factors for 90Y in spheroids from 0.1 to 1 g; 2) correcting for cross-organ radiation; and 3) using actual mouse anatomy as represented by nuclear magnetic resonance imaging with a three-dimensional internal dosimetry package (3D-ID). RESULTS: The kidney was the first dose-limiting organ with the use of Fab fragments. Acute radiation nephritis occurred at injected activities > or = 325 microCi, and chronic nephrosis at doses > or = 250 microCi. Activities of 200 microCi were tolerated by 100% of the animals (i.e., the MTD). Application of lysine decreased the renal dose by approximately fivefold, facilitating a 25% increase in the MTD (to 250 microCi), because myelotoxicity became dose-limiting despite red marrow doses of less than 5 gray (Gy). By using BMT and lysine, the MTD could be doubled from 200 to 400 microCi, where no biochemical or histologic evidence of renal damage was observed (kidney dose, < or = 40 Gy). With injected activities of > or = 325 microCi without kidney protection, and with a hepatic self-to-self dose of only 4 Gy, rising liver enzymes were observed, which could be explained only by cross-organ radiation from radioactivity in the kidneys (in the immediate neighborhood of the right kidney up to > or = 150 Gy). The MTD of F(ab)2 fragments could be elevated only by a combination of BMT and lysine. With IgG, the bone marrow alone was dose-limiting. Tumor dosimetry correlated well with antitumor effects; Fab was more effective than F(ab)2, which was consistent with its more favorable dosimetry, and it may also be more effective than IgG due to its higher dose rate and more homogenous distribution. Dosimetry Model 1 was insufficient for predicting biologic effects. Model 2 seemed to

be more accurate, accounting for interorgan crossfire. However, Model 3 showed an additional substantial contribution to the red bone marrow dose due to crossfire from the abdominal organs. CONCLUSIONS: These data show that radiation nephrotoxicity is an important effect of cancer therapy with radiometal-conjugated antibody fragments or peptides. However, this effect can be overcome successfully with the application of cationic amino acids, which substantially increase the anti-tumor efficacy of radiometal-labeled immunoconjugates. For understanding the biologic effects (e.g., liver toxicity) of 90Y in a mouse model, accounting for cross-organ radiation is essential. Further studies with radiometal-conjugated monoclonal antibody fragments and peptides are necessary to determine the MTD, dose-limiting organs, antitumor effectiveness, and nephroprotective effects of cationic amino acids in humans.

L11 ANSWER 8 OF 19 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 1998090337 MEDLINE
DOCUMENT NUMBER: 98090337
TITLE: **D-lysine** reduction of indium-111 octreotide and yttrium-90 octreotide **renal uptake**.
AUTHOR: Bernard B F; Krenning E P; Breeman W A; Rolleman E J; Bakker W H; Visser T J; Macke H; de Jong M
CORPORATE SOURCE: Department of Nuclear Medicine, Erasmus Medical University and Academic Hospital Dijkzigt, Rotterdam, The Netherlands.
SOURCE: JOURNAL OF NUCLEAR MEDICINE, (1997 Dec) 38 (12) 1929-33.
Journal code: JEC. ISSN: 0161-5505.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199804
AB Indium-111-DTPA-octreotide (111In-DTPAOC) is used successfully for imaging somatostatin receptor-positive lesions. A new and promising application is its use in peptide-receptor radionuclide therapy (PRRT). For the latter purpose, [DOTA0,D-Phe1,Tyr3]octreotide (DOTATOC), which is suitable for stable radiolabeling with 90Y, is probably even more promising. Significant **renal uptake** of these octreotide analogs exists, however, reducing the scintigraphic sensitivity for detection of small tumors in the perirenal region and limiting the possibilities for PRRT. We showed that the **renal uptake** of 111In-DTPAOC could be reduced to about 50% of control by **L-lysine administration** in vivo in rats. This study compares the effects of several doses and different methods of **administration** of D- and **L-lysine**, in addition to time-related effects of **D-lysine**, on

kidney uptake of 111In-DTPAOC and 90Y-DOTATOC. METHODS: Male Wistar rats (200-250 g) were given 111In-DTPAOC (0.2 MBq, 0.5 microg-0.5 mg intravenously, intraperitoneally or orally) in the presence or absence of D- or **L-lysine**. At 1, 4 or 24 hr, the rats were killed, and the organs were isolated and counted for radioactivity. In different experiments, male Wistar rats (200-250 g) were given 90Y-DOTATOC (1 MBq, 0.5 microg intravenously) in the presence or absence of **D-lysine**. At 24 hr, the rats were killed, and the organs were isolated and counted for radioactivity. RESULTS: **Administration** of D- or **L-lysine** in a single intravenous dose of 400 mg/kg, resulted in more than 50% inhibition of **kidney uptake** of 111In-DTPAOC at all time points tested, independently of the mass of 111In-DTPAOC used. Higher or repeated doses of lysine did not give a significantly higher percentage inhibition. **D-lysine**, given orally in a dose of 400 mg/kg at 30 or 15 min before 111In-DTPAOC injection, resulted in 30% and 20% inhibition of **kidney uptake**, respectively. **L-lysine**, given orally 30 min before 111In-DTPAOC **administration**, resulted in 30% inhibition as well. Inhibition of **kidney uptake** of 111In-DTPAOC by **L-lysine** after intraperitoneal **administration** was 40%. After **L-lysine administration**, 111In-DTPAOC was decreased in the kidneys and in somatostatin receptor-positive organs such as the pancreas and adrenal glands. In contrast, **D-lysine** did not have a significant effect on **uptake** in octreotide receptor-positive organs. **Renal uptake** of 90Y-DOTATOC was reduced by 65% by intravenous **D-lysine**, whereas radioactivity in blood, pancreas and adrenal glands was not affected. CONCLUSION: **D-lysine** may be preferred to **L-lysine** for reduction of **renal uptake** of radioactivity during scintigraphy and PRRT because of its lower toxicity and because it should not interfere with the natural amino acid metabolic balance.

L11 ANSWER 9 OF 19 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 97388465 MEDLINE
DOCUMENT NUMBER: 97388465
TITLE: Differential inhibitory effect of **L-lysine** on renal accumulation of 67Cu-labelled F(ab')2 fragments in mice.
AUTHOR: Rutherford R A; Smith A; Waibel R; Schubiger P A
CORPORATE SOURCE: Division of Radiopharmacy, Paul Scherrer Institute, Villigen, Switzerland.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1997 Jul 29) 72 (3) 522-9.
Journal code: GQU. ISSN: 0020-7136.
Searcher : Shears 308-4994

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199710
ENTRY WEEK: 19971005

AB The basic amino acid **L-lysine** was **administered** to mice in an attempt to circumvent unwanted renal accumulation of 67Cu-labelled F(ab')2 fragments derived from the anti-NCAM IgG1, SEN7 and anti-CEA IgG1 monoclonal antibody (MAb)35. In control experiments, significant **renal uptake** of both 67Cu-labelled F(ab')2 fragments was observed, radiolabel being primarily localised to proximal tubules in the renal cortex. Following optimised **L-lysine** dosing protocols, **renal uptake** of 67Cu-MAb35 F(ab')2 was inhibited by up to 42%. Surprisingly, little inhibition (< 10%) of 67Cu-SEN7 F(ab')2 uptake was observed. Experiments to investigate this differential inhibition indicated that inhibition of MAb35 F(ab')2 uptake was relatively short-lived (approx. 6 hr), whilst no apparent differences were found in blood clearance rates between either 67Cu-F(ab')2 fragment. **L-lysine** **administration** caused a significant diuresis with high levels of intact 67Cu-labelled SEN7 and MAb35 F(ab')2 appearing in the urine, possibly due to blockade of **renal** **uptake** and lysine-induced increases in glomerular membrane permeability. Iso-electric focusing studies failed to identify any charge differences between the 67Cu-labelled F(ab')2 fragments, although a cathodal migration of all 67Cu-labelled samples, presumably due to the net positive charge conferred by addition of 67Cu2+ ions, was observed. Our results demonstrate that in addition to net charge, other unidentified characteristics may influence renal accumulation of radiometal-labelled F(ab')2 fragments and their inhibition by **L-lysine**.

L11 ANSWER 10 OF 19 JICST-EPlus COPYRIGHT 2000 JST
ACCESSION NUMBER: 970898252 JICST-EPlus
TITLE: Animal studies on the reduction and/or dilution of 2-deoxy-2-.cents.18F!fluoro-D-glucose (FDG) activity in the urinary system.
AUTHOR: KOSUDA S; FISHER S; WAHL R L
CORPORATE SOURCE: Univ. Michigan Medical Center Univ. Hpspital
SOURCE: Ann Nucl Med, (1997) vol. 11, no. 3, pp. 213-218.
Journal Code: X0838A (Fig. 4, Ref. 37)
CODEN: ANMEEX; ISSN: 0914-7187
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
LANGUAGE: English
STATUS: New

AB To evaluate two methods for decreasing and/or diluting the FDG

activity in the urinary system, five rats were intraperitoneally given 1,000.MU.g/g of **L-lysine** 4 times, starting from 60 minutes before iv injection of FDG, and then at 30-minute intervals for 90 minutes. Five rats were used as controls. In a furosemide study, 12 rats were allocated to three groups. Group 1 received iv injection of FDG alone. Group 2 received saline before iv injection of FDG. Group 3 received furosemide (7 mg/kg) and saline (1/30 of body weight). Neither **renal uptake** nor urinary excretion of FDG had a statistically significant difference: **renal uptake**; 0.179.+-.0.011 (**L-lysine**) vs.0.119.+-.0.003 (control) % kg injected dose/g. The % dose excreted and total urine volume were: 15.0.+-.2.5 to 15.5.+-.2.5 with 2.98 ml (**L-lysine**), 22.9.+-.1.8 to 24.2.+-.1.5 with 1.41 ml (control). The furosemide study revealed a statistically significant difference: Group 1; 7.57.+-.4.73, Group 2; 0.686.+-.0.638, Group 3; 2.37.+-.2.33% kg injected dose/g ($p<0.01$ for Group 1 vs.Group 2, $p<0.05$ for Group 1 vs. Group 3). While pretreatment with **L-lysine** or furosemide failed to decrease renal activity of FDG, saline injection without furosemide markedly decreased urinary activity. (author abst.)

L11 ANSWER 11 OF 19 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1996-454840 [45] WPIDS
DOC. NO. CPI: C1996-142505
TITLE: Reducing **renal uptake** of antibody fragment conjugate - using **D-lysine** or poly-D- or **L-lysine**, for reducing radio-label or cytotoxic agent uptake in assay or therapy.
DERWENT CLASS: B04 B05
INVENTOR(S): BEHR, T M; GOLDENBERG, D M
PATENT ASSIGNEE(S): (MOLE-N) CENT MOLECULAR MEDICINE & IMMUNOLOGY
COUNTRY COUNT: 71
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9629087	A1	19960926	(199645)*	EN	39
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG					
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN					
AU 9653616	A	19961008	(199704)		
EP 767673	A1	19970416	(199720)	EN	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
JP 10505866	W	19980609	(199833)		34
US 5843894	A	19981201	(199904)		

AU 700346 B 19990107 (199913)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9629087	A1	WO 1996-US3308	19960320
AU 9653616	A	AU 1996-53616	19960320
EP 767673	A1	EP 1996-910422	19960320
		WO 1996-US3308	19960320
JP 10505866	W	JP 1996-528465	19960320
		WO 1996-US3308	19960320
US 5843894	A	US 1995-407899	19950321
AU 700346	B	AU 1996-53616	19960320

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9653616	A	Based on	WO 9629087
EP 767673	A1	Based on	WO 9629087
JP 10505866	W	Based on	WO 9629087
AU 700346	B	Previous Publ.	AU 9653616
		Based on	WO 9629087

PRIORITY APPLN. INFO: US 1995-407899 19950321

AN 1996-454840 [45] WPIDS

AB WO 9629087 A UPAB: 19961111

Use of 1 cpd. (I) selected from **D-lysine**, poly-**D-lysine**, poly-**L-lysine** and their salts and carboxyl derivs. is claimed for reducing **kidney uptake** of antibody (Ab) fragment conjugates or radiolabelled Ab fragments, in a radioimmunodiagnosis or immunotherapy involving injection of an Ab fragment conjugate or radiolabelled Ab fragment. Also claimed is the use of (I) for prepn. of an agent for use as above.

(I) is **administered** parenterally (specifically by continuous infusion or by 1 bolus injection) in aq. soln., or orally. The poly-D- or -**L-lysine** has mol. wt. 15-30 kDa. The AB fragment conjugate is radiolabelled (esp. with an imaging isotope for use in radioimmunodiagnosis) or contains a cytotoxic agent for use in immunotherapy.

ADVANTAGE - **Admin**. of (I) markedly reduces **renal uptake** and **retention** of radioisotopes (which can reduce diagnostic accuracy, as well as causing radiation nephritis) and cytotoxic agents (which can cause kidney damage). (I) are less toxic, and require fewer and lower doses than prior art agents. Typically (I) reduce **renal uptake** and **retention** of radioisotopes by a factor

of 3, allow clear detection and imaging of a tumour or infectious lesion otherwise obscured by high background radiation around the kidney (esp. when using short imaging times of 1-5 hrs.) and allow use of a 2-3 fold higher dose of conjugate than could otherwise be used without risk of kidney damage.
Dwg.0/7

L11 ANSWER 12 OF 19 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 96328104 MEDLINE
DOCUMENT NUMBER: 96328104
TITLE: **L-lysine** effectively blocks **renal uptake** of 125I- or 99mTc-labeled anti-Tac disulfide-stabilized Fv fragment.
AUTHOR: Kobayashi H; Yoo T M; Kim I S; Kim M K; Le N; Webber K O; Pastan I; Paik C H; Eckelman W C; Carrasquillo J A
CORPORATE SOURCE: Department of Nuclear Medicine, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892-1180, USA.
SOURCE: CANCER RESEARCH, (1996 Aug 15) 56 (16) 3788-95. Journal code: CNF. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199611
AB In this study, we investigated the ability of **L-lysine** to block **renal uptake** of 125I- or 99mTc- labeled Fv fragments. Anti-Tac disulfide-stabilized Fv fragment (dsFv) was derived from a murine monoclonal antibody that recognizes the alpha subunit of the interleukin-2 receptor (IL-2R alpha). The 125I- or 99mTc-labeled dsFv was injected i.v. into non-tumor-bearing nude mice or into nude mice bearing SP2/Tac (IL-2R alpha positive) and SP2/0 (IL-2R alpha negative) tumor. We then evaluated the pharmacokinetics of L-[3H]lysine and the effect of **L-lysine** dose, timing of **administration**, and route of delivery on catabolism and biodistribution of i.v. dsFv. Peak **renal uptake** of i.v. or i.p. injected L-[3H]lysine occurred within 5 and 15 min, respectively. The **kidney uptake** of **L-lysine** exhibited a dose-response effect. When **L-lysine** was coinfused or injected shortly before dsFv, **renal uptake** of dsFv was blocked to < 5% of the control, but longer intervals were less effective. Aminosyn II and Travasol 10% (parenteral amino acid solutions) also blocked **renal uptake** of radiolabeled dsFv. **Administration** of **L-lysine** did not alter the blood kinetics and slightly increased the tumor uptake of dsFv, but it did prevent

catabolism in the kidney and resulted in lower amounts of catabolites in the serum and urine. In conclusion, we have shown that a blocking dose of lysine, injected with or immediately before the injection of radiolabeled dsFv, is most effective in blocking the **renal uptake** of dsFv. This is consistent with the rapid uptake of L-[3H]lysine by the kidney and is further substantiated by the relative ineffectiveness of lysine injected immediately after the radiolabeled dsFv injection.

L11 ANSWER 13 OF 19 MEDLINE
ACCESSION NUMBER: 95368640 MEDLINE
DOCUMENT NUMBER: 95368640
TITLE: Reduction of the **renal uptake** of radiolabeled monoclonal antibody fragments by cationic amino acids and their derivatives.
AUTHOR: Behr T M; Sharkey R M; Juweid M E; Blumenthal R D; Dunn R M; Griffiths G L; Bair H J; Wolf F G; Becker W S; Goldenberg D M
CORPORATE SOURCE: Garden State Cancer Center, Center for Molecular Medicine and Immunology, Newark, New Jersey 07103-2763, USA.
CONTRACT NUMBER: CA39841 (NCI)
SOURCE: CANCER RESEARCH, (1995 Sep 1) 55 (17) 3825-34. Journal code: CNF. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199511
AB The **renal uptake** of radiolabeled antibody fragments and peptides is a problem in radioimmunodetection and radioimmunotherapy, especially with intracellular retained radiometals. The aim of this study was to develop suitable methods to reduce this **kidney uptake**. BALB/c mice or nude mice bearing the human GW-39 colon carcinoma xenograft were given i.p. injections of basic amino acids or a range of different basic amino acid derivatives, amino sugars, as well as cationic peptides. The effect of these agents on the biodistribution of Fab' and F(ab')2 fragments of different mAbs radiolabeled with 99mTc, 188Re, 111In, 88Y, or 125I was studied. Tumor and organ uptake was determined and compared to untreated mice. The **kidney uptake** of Fab' fragments was reduced 5-6-fold in a dose-dependent manner as compared to untreated controls. The uptake in all other organs, as well as the tumor, was unaffected. A similar reduction in **renal retention** was seen for all other intracellularly retained isotopes, as well as for F(ab')2 fragments. D- and L-isomers of lysine were equally effective whether given i.p. or p.o. D-glucosamine was effective, but its N-acetyl derivative was not. Basic polypeptides (e.g., poly-L-

lysine) were also effective; their potency increased with increasing molecular weight. HPLC of the urine taken from treated animals showed the excretion of intact Fab', in contrast to mostly low-molecular-weight metabolites in the control group. These studies indicate that a variety of basic compounds is capable of inhibiting the tubular reabsorption of peptides and proteins, thus lowering the **kidney uptake** of antibody fragments significantly.
On a molecular basis, the effect seems to essentially rely on the presence of a positively charged amino group. By reducing **renal retention** of antibody fragments, their role as imaging and therapeutic agents may be expanded.

L11 ANSWER 14 OF 19 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96015589 EMBASE
DOCUMENT NUMBER: 1996015589
TITLE: Gamma scintigraphy of 111In-labelled branched chain polypeptides (BCP) with a poly(**L-lysine**) backbone in mice with mammary carcinoma: Effect of charge on biodistribution and tumour imaging potential.
AUTHOR: Pimm M.V.; Perkins A.C.; Gribben S.J.; Mezo G.; Gaal D.; Hudecz F.
CORPORATE SOURCE: Department of Medical Physics, University Hospital,Nottingham NG7 2UH, United Kingdom
SOURCE: Annals of Nuclear Medicine, (1995) 9/4 (247-251). ISSN: 0914-7187 CODEN: ANMEEX
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
023 Nuclear Medicine
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Radiolabelled synthetic branched chain polypeptides (BCP) represent a new and novel range of materials with potential as radiopharmaceuticals. Preliminary imaging studies have been undertaken with 111In-labelled BCP in mice with subcutaneously transplanted mammary carcinoma. Four polypeptides each with a poly(**L-lysine**) backbone and side chains of DL-alanine residues were studied. These were AK, which is polycationic, EAK which is amphoteric, having additional glutamic acid residues at the end of the side chains, and AcEAK (anionic) and SucEAK (highly polyanionic) where the terminal glutamic acid amino groups were acetylated or succinylated respectively. Radiolabelling was achieved by previous conjugation with DTPA. Serial images up to 48 hours showed marked retention of 111In-labelled polycationic AK and polyanionic SucEAK in the liver and spleen, with **renal uptake** also being visible in the case of AK. 111In-labelled EAK and AcEAK showed longer blood survival with some liver uptake,

but tumour uptake was also visualized by 24 hours with both of these polypeptides. These studies demonstrate the feasibility of using 111In-labelled synthetic branched chain polypeptides as radiopharmaceuticals for gamma scintigraphy and the visualization of tumours by modification of the side chain structure. These materials warrant further study.

L11 ANSWER 15 OF 19 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94320705 EMBASE
DOCUMENT NUMBER: 1994320705
TITLE: Application of high affinity binding concept to radiolabel avidin with Tc-99m labeled biotin and the effect of pI on biodistribution.
AUTHOR: Jeong J.M.; Kinuya S.; Paik C.H.; Saga T.; Sood V.K.; Carrasquillo J.A.; Neumann R.D.; Reynolds J.C.
CORPORATE SOURCE: Department of Nuclear Medicine, Warren G. Magnuson Clinical Center, National Institutes of Health,Bethesda, MD 20892, United States
SOURCE: Nuclear Medicine and Biology, (1994) 21/7 (935-940). ISSN: 0969-8051 CODEN: NMBIEO
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
023 Nuclear Medicine
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB In order to label avidin with Tc-99m, we took advantage of the high affinity binding of biotin to avidin; we radiolabeled a biotin derivative with Tc-99m and then bound this Tc-99m labeled biotin derivative to avidin. For our labeling approach, N.epsilon.-biotinyl-**L-lysine** (Biocytin) was reacted with the N-hydroxysuccinimide ester of benzoylmercaptoacetyltriglycine (Bz-MAG3). The resulting Bz-MAG3-Biocytin was labeled with Tc-99m using Tc-99m glucarate as a Tc-99m transchelating agent and mixed with avidin at a 1:1 molar ratio resulting in almost a quantitative labeling yield. Tc-99m-MAG3-Biocytin/Avidin was stable in serum at 37.degree.C with 97 and 95% of the total Tc-99m activity still bound to avidin at 2 and 24 h, respectively. The biodistribution of Tc-99m-MAG3-Biocytin/Avidin in normal Balb/c mice showed a high liver and **kidney uptake** with 56.6 and 28.9%, respectively at 10 min. We attempted to lower the liver and the kidney activities by reducing the isoelectric point (pI) of avidin by conjugating succinic acid moieties at lysine residues of avidin (pI 10). The **kidney uptake** decreased to 19.0, 3.1 and 1.7% when the pI of avidin was reduced to 7.0-9.3, 5.5-6.2 and 4.0-4.8, respectively. The lowering of the pI, however, did not change the